Remarks/arguments

Claims 45-58 are pending.

Provisional Rejections for Obviousness-type Double Patenting

Claims 45 and 47-58 have been provisionally rejected for obviousness-type double patenting over claims 1-3, 5, 7, 8, 12-17, 43-46, 48, and 49 of co-pending Application No. 10/510,673. The previously submitted terminal disclaimer was not approved because it did not comply with 37 CFR 1.321(c)(3). This rejection should be withdrawn in view of the compliant terminal disclaimer submitted with this paper.

Claims 45, 46, 49-51, and 57 have been provisionally rejected for obviousness-type double patenting over claims 27, 39-47, and 50-52 of co-pending Application No. 11/885,288. The previously submitted terminal disclaimer was not approved because it did not comply with 37 CFR 1.321(c)(3). This rejection should be withdrawn in view of the compliant terminal disclaimer submitted with this paper.

Rejections under 35 U.S.C. § 103(a)

Claims 45-58 have been rejected as obvious over WO 99/32119 (Kaiko) in view of U.S. Patent No. 3,773,955 (Pachter).

According to the Examiner, Kaiko teaches:

- an oral dosage form comprising an opioid agonist and an opioid antagonist in a ratio that is analgesically effective when administered, but aversive in physically dependent subjects;
- sustained release via incorporation of a sustained release carrier into a matrix or a sustained release coating;

- naloxone in an amount that is equi-antagonistic to naltrexone, and naloxone doses of 0.8 mg – 24 mg;
- oxycodone and pharmacologically acceptable salts or esters thereof; and
- prior art oxycodone-naloxone compositions having a ratio of 2.5-5:1 parts by weight.

The Examiner acknowledges that Kaiko does not teach a pharmaceutical preparation containing oxycodone-naloxone with the specific weight ratio of 2:1 or a preparation in the form of specific pharmaceutically acceptable and equally active free base salts.

According to the Examiner, Pachter discloses:

- an oral analgesic composition comprising an orally inactive dose of naloxone and an analgesic, including oxycodone;
- oxycodone to naloxone ratios of 2-20 parts to 1; and
- that the analgesic can be any of the pharmaceutically acceptable nontoxic salts.

The Examiner contends that it would have been obvious to administer the oxycodone-naloxone dosage in the formulation of Kaiko in a ratio of 2:1 because Pachter teaches that such a ratio provides an effective analgetic composition that negates the euphoria and physical dependence of the composition.

Applicants respectfully traverse this rejection. Support for Applicants' traversal is provided in the attached Declaration Under 37 CFR 1.132 by Dr. Michael Hopp ("the Hopp Declaration", attached as **Exhibit A**).

Since June 2010, Dr. Hopp has held the position of Head of Medical Science Pain at Mundipharma Research GmbH & Co. KG ("Mundipharma"). From January 2001 to June 2010, Dr. Hopp was a European medical research physician responsible for planning and performing

clinical studies for Mundipharma. A copy of Dr. Hopp's curriculum vitae is attached as **Exhibit B**. Mundipharma is associated with the instant assignee, Euro-Celtique S.A

Opioids such as oxycodone provide analgesia and are often first-line treatment for patients suffering from severe pain, such as cancer pain. Hopp Declaration at 9; Meissner et al., Eur J Pain, 2009;13:56-64, 56 ("Meissner") (Exhibit D to the October 13, 2009 Response). Gastrointestinal (GI) adverse effects associated with opioid (e.g., oxycodone) administration include, for example, constipation, nausea, spasms, cramps, bloating and abdominal pain. Hopp Declaration at 10; Meissner, p. 56. The GI adverse effects associated with oxycodone administration are common and can be severe. Hopp Declaration at 11. The frequency and/or severity of the GI side effects can result in patient non-compliance and undertreatment. Hopp Declaration at 12; Meissner, p. 56.

The instant invention is directed to a pharmaceutical preparation comprising a combination of oxycodone and/or its pharmaceutically acceptable salts, and naloxone and/or its pharmaceutically acceptable salts, in a controlled release matrix providing sustained release, wherein the oxycodone and/or its pharmaceutically acceptable salts, and naloxone and/or its pharmaceutically acceptable salts are in a weight ratio of 2:1; the naloxone and/or its pharmaceutically acceptable salts is present in an amount of about 1 to about 50mg and the oxycodone and/or its pharmaceutically acceptable salts is present in an amount of about 10 to about 150mg. The instant claims recite critical dosage amounts and active ingredient weight ratios, which minimize GI side effects without compromising the beneficial analgesic effect of oxycodone and/or its pharmaceutically acceptable salts. Hopp Declaration at 17, 19, 21, 24.

The Examiner acknowledges that Kaiko does not teach a 2:1 oxycodone to naloxone parts by weight ratio. Pachter discloses a wide range of oxycodone to naloxone ratios (2:1 to

20:1). Thus, the claimed ratio coincides with the extreme lower limit of the range of ratios disclosed in Pachter. Nothing in Pachter (or in Kaiko) indicates, expressly or by implication, that the claimed 2:1 ratio imparts unexpected benefits compared to other ratios. Hopp Declaration at 17, 24. A *prima facie* case of obviousness based on overlapping ranges can be overcome by showing the criticality of the claimed range. MPEP 2144.05; *In re Woodruff*, 919 F.2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990). Here, the "overlap" is a single ratio, 2:1, and the claim is not to a range, but to the single ratio. A showing of criticality of the claimed ratio would therefore encompass the entire scope of the claim and overcome the *prima facie* obviousness rejection.

In the October 13, 2009 Response, Applicants provided clinical evidence that among patients who received oxycodone and naloxone in parts by weight ratios ranging from 1:1 to 8:1, those who received the drugs in a ratio of 2:1 did the best when all aspects of treatment were taken into account, i.e., reduction of pain intensity, improvement in bowel function index, occurrence of adverse effect, avoidance of diarrhea, tolerability and preference.

Exhibit D to the October 13, 2009 Response is Meissner et al., Eur J Pain, 2009:13:56-64 (Meissner). In this peer-reviewed journal, Meissner describes a multi-center, prospective, placebo-controlled, randomized, double-blind, parallel group clinical trial of male and female patients with severe, chronic pain who required opioid treatment. One hundred and sixty-six patients completed the trial. Treatment groups received oxycodone and naloxone in ratios of 1:1, 1.5:1, 2:1, 3:1, 4:1, 6:1, and 8:1. The trial was designed and sponsored by Mundipharma GmbH, a company associated with the instant assignee, Euro-Celtique S.A.[1] The trial showed that an oxycodone to naloxone ratio of 2:1 improved bowel function relative to the higher ratios, with an approximately 50% improvement over the 4:1 ratio treatment. Further, the improvement was not associated with any lessening of the effect on pain intensity relative to other ratios, nor any

[1] Thus, the Meissner authors may have received compensation from Mundipharma.

increase in adverse effects. Meissner, p. 62. Additional evidence submitted with the October 13, 2009 Response corroborated the superiority of the 2:1 ratio. *See,* Amendment filed October 13, 2009, p. 5-6 and Exhibits. A-E thereto.

The Examiner was not persuaded by this evidence, stating that:

> While the applicant is arguing the preparation containing oxycodone and naloxone for improvement of a patient's bowel function ... the claims are directed to a pharmaceutical composition .... Because the claims are directed to a pharmaceutical composition, then a prior art which anticipates or renders obvious the aforementioned drugs in the aforementioned ratios and ranges will necessarily meet the limitation of the claim regardless of the effect such composition may have on a patient's bowel function.

Office Action, p. 3-4. Respectfully, applicants did not put forward the evidence to import a limitation into the claims (e.g., a composition that improves bowel function) or assert that an intended result (e.g., improved bowel function) limits the composition claims and excludes prior art. Rather, the evidence shows that the claimed 2:1 ratio is critical. As Meissner concluded from the trial results:

> The availability of a strong opioid with an improved tolerability profile, such as a fixed 2:1 oxycodone/naloxone combination, has significant added therapeutic value, thus representing a major advance in the treatment and quality of life of patients suffering from sever chronic pain.

Meissner, p. 64.

Further, one of ordinary skill in the art could not have reasonably predicted that the claimed 2:1 ratio is the optimal, critical ratio. Hopp Declaration at 17, 24. For example, patients administered oxyocodone/naloxone in a ratio of 1.5:1 had a 50% incidence of diarrhea compared to a 29.4% incidence in patients administered oxycodone/naloxone in the claimed 2:1 ratio. Meissner, p. 63, 2nd para. Thus, this small decrease in the ratio resulted in a clinically significant increase in GI adverse effects. *Id.*, Hopp Declaration at 21-24.

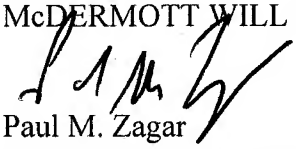
For the reasons stated above, the instantly claimed 2:1 ratio is a critical value that coincides with the lower-most limit of the prior art range. The criticality of the claimed ratio is sufficient to overcome the *prima facie* obviousness rejection. Accordingly, this rejection should be withdrawn.

Conclusion

This application is believed to be in condition for allowance. If any issues remain which may be addressed by an Examiner's amendment or a supplemental amendment, the Examiner is respectfully requested to contact the undersigned.

Respectfully submitted,

McDERMOTT WILL & EMERY LLP



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